Refer to: Crohn disease—Newer aspects of etiology, diagnosis and therapy—Medical Staff Conference, University of California, San Francisco. West J Med 128:419-427, May 1978

Crohn Disease

Newer Aspects of Etiology, Diagnosis and Therapy

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and Robert C. Siegel, Associate Professor of Medicine and Orthopaedic Surgery, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. MORRELLI:* *This morning's Medical Grand Rounds will be led by Dr. John P. Cello from the Gastrointestinal Unit at San Francisco General Hospital Medical Center.*

DR. CELLO:† In a report published in 1932 in the *Journal of the American Medical Association,* Crohn, Ginzberg and Oppenheimer[1] described and classified a new pathologic and clinical entity that they called "regional ileitis."[1] They described a granulomatous process in the terminal ileum that mainly occurs in young adults and is characterized by a subacute or chronic cicatrizing inflammation. This disease entity, now called "Crohn disease," was actually first described in 1806 by Coombe and Saunders at the Royal College of Physicians in London.[1]

Tremendous strides have been made in our understanding of the clinical aspects of Crohn disease of the bowel over the past few years. We would like to put into perspective the exciting newer developments in Crohn disease, particularly studies on causes and pathogenesis, newer methods of laboratory diagnosis, improvements in diagnostic radiography and advances in the medical therapy.

*Howard Morrelli, MD, Professor of Medicine.

†John P. Cello, MD, Assistant Professor of Medicine; Chief, Clinical Gastroenterology, San Francisco General Hospital Medical Center.

Etiology

Studies of the pathogenesis of Crohn disease have taken two main paths: *first,* a search for infectious agents, either serologic markers of the agents in the host or isolation *in vitro,* or transmission of the agents to experimental animals; *second,* an attempt to define possible host susceptibility factors that make a portion of the population at risk of Crohn disease developing.

Neither of these avenues of research has produced totally convincing evidence of Crohn disease as an infectious or inherited disease, but the research in this area is provocative.

Search for Infectious Agents

Aerobic, anaerobic, and mycobacterial cultures of bowel specimens from patients with Crohn disease have failed to show any unique organism. The study by Farmer and associates illustrates

ABBREVIATIONS USED IN TEXT
ACTH = adrenocorticotropin
CDAI = Crohn disease activity index
DNCB = dinitrochorobenzene
HLA = human leukocyte A (histocompatibility antigen)
6-MP = 6-mercaptopurine
RNA = ribonucleic acid
SKSD = streptokinase and streptodornase

the search for a viral cause of the disease.[2] In a comparison of 15 patients with Crohn disease with 65 age-matched and sex-matched control subjects, there was no difference in results of serologic tests for a number of viruses between the two groups. In addition, tissue cultures for cytopathogenic viruses failed to show any consistent changes. Some other viral investigations showed differences in the Crohn population, but they have not been confirmed. Recently, electron microscopic, physical and biochemical studies were carried out by Gitnik and Rosen[3] on viral isolates from tissue from patients with Crohn disease in Vermont, England and California; tissue from surgical patients served as the control. The same cytopathic changes occurred in patients from these three areas but not in control groups. Electron microscopic studies showed 90 nm viral-like particles in tissues from patients with the disease from all three areas, but not in the control cultures. These and a few other reports suggest a viral cause for the disease.

Some of the most provocative studies purporting to show a transmissible agent in Crohn disease have come from *in vivo* inoculation studies in which fresh homogenates of Crohn disease tissue have been injected intravenously or intraperitoneally, or into the ileum or footpad of experimental animals.[4-7] The tissues homogenized for the transmission studies had characteristics of classic Crohn disease: thickened bowel wall, deep longitudinal ulcerations and thickened serosal fat (creeping fat). Most researchers used 0.2 μ to 100 μ filtrates of homogenates of a full thickness of fresh bowel wall obtained from patients with active Crohn disease at operation and injected the material into many sites in various animals. In one study,[4] a single inoculum of 0.2 μ to 100 μ filtrates introduced into the ileum of rabbits produced macroscopic changes within nine months similar to those in human Crohn disease. These changes did not occur in rabbits injected with homogenates of normal bowel.

Further evidence for the transmissibility of Crohn disease was obtained from *serial passage* studies in which ileal tissue of rabbits, inoculated many months earlier with a filtrate of homogenates from human Crohn disease tissue, and showing macroscopic and microscopic changes suggestive of Crohn disease, was homogenized and injected into the ileum of other rabbits.[4] Again after a nine-month latency period, nearly 50 percent of these rabbits had changes similar to those of Crohn disease, whereas no changes were observed in any of the control rabbits. Transmission of the macroscopic changes does not occur when the homogenates are subjected to irradiation with cobalt 60, freezing to less than $-20°C$, or autoclaving. These studies suggest that the causative agent is a viable organism that is smaller than 0.2 μ or is capable of deformation so that it can pass through the 0.2 μ filter—that is, either a virus or an L-form of bacterium. Numerous investigators have shown the induction of macroscopic noncaseating, granulomatous changes in other species, such as mice and guinea pigs, after intraperitoneal, intravenous and intradermal injection of filtrates of Crohn disease tissue. Furthermore, the changes were subsequently induced in other animals after two serial animal passages, again suggesting that a transmissible agent is involved in the cause of Crohn disease.

Studies using 0.2 μ filtrates of Crohn disease tissue cultured in hypertonic media have shown growth of a cell wall-defective (L-form) pseudomonas in a large number of patients with Crohn disease.[8] No L-forms were isolated from tissue taken from patients with ulcerative colitis or control subjects. Although these results strongly suggest that a transmissible agent is involved in the cause of Crohn disease, several problems arise: the number of patients and control subjects was small in many of the studies and, more important, the results cannot be replicated in other laboratories. Therefore, despite the data indicating that a unique transmissible viral-like agent might exist, evidence of a transmissible agent in Crohn disease is not clear-cut at present but appears likely.

Host Factors

Numerous investigations of host factors have been carried out in patients with Crohn disease and their blood relatives. The best studies show no difference in HLA-A or HLA-B antigens (histocompatibility antigens) in patients with Crohn

disease.[9] However, it has been well documented that a high frequency of certain HLA antigens occurs in some patients with extensive disease and certain associated conditions. For example, patients with ankylosing spondylitis or sacroiliitis have a higher incidence of HLA B-27 antigen than other patients with Crohn disease. In addition, patients with HLA B-27 antigen may have a higher incidence of pancolonic involvement with either Crohn disease or ulcerative colitis.

Earlier studies suggested that immunologic competence is altered to a pronounced degree *in vivo* in patients with active Crohn disease, but this is now controversial.[10] In the initial studies, the incidence of sensitivity to purified protein derivative was considerably decreased in patients with Crohn disease, suggesting altered delayed hypersensitivity. Other studies suggested that skin reactivity to dinitrochorobenzene (DNCB) and to mumps, Candida, and streptokinase and streptodornase (SKSD) antigens was altered. However, the most recent studies showed that in patients *not taking steroids* skin sensitization to DNCB, mumps, Candida and SKSD antigens is normal. This indicates a normal delayed hypersensitivity immune mechanism. Furthermore, absolute serum levels of immunoglobulins were normal except for the diffuse increase in immunoglobulins during the acute flare state. *In vitro* immunologic studies of patients with Crohn disease have also yielded conflicting results.[11] In an excellent recent review[12] of lymphocytes and cutaneous anergy in 33 patients with Crohn disease who were not taking steroids, the mean total lymphocyte count was within normal limits, but the mean absolute peripheral T-lymphocyte count was reduced and the mean absolute peripheral B-lymphocyte count was elevated. Of the patients, 86 percent were anergic in their ability to become sensitized to DNCB compared with 9 percent of the normal control subjects. This indicates lymphocyte hyporesponsiveness in patients with Crohn disease.

In vitro studies of the isolated peripheral lymphocytes in patients with Crohn disease have yielded interesting results. Stobo and his group studied the *in vitro* cytotoxicity of lymphocytes in patients with inflammatory bowel disease.[13] They were able to show that isolated mononuclear cells of peripheral blood can lyse *in vitro* allogeneic colonic epithelial cells. The cells responsible for the colonic cell lysis are probably killer "K" or null cells with a surface receptor for F_c and not T or B cells. This study found the occurrence of an antibody-dependent cell-mediated cytotoxicity, that can be shown *in vitro,* in patients with inflammatory bowel disease.

Korsmeyer reported for the first time the presence of lymphocytotoxic and double-stranded ribonucleic acid (RNA) antibodies in patients with inflammatory bowel disease.[14,15] A higher percentage of patients with Crohn disease and their families (their first degree relatives who are household contacts and their spouses) had a higher incidence of lymphocytotoxic antibody than normal control subjects.[14] Antibody to double-stranded RNA was also found in a higher percentage of patients and families with Crohn disease than in control subjects.[15] Conflicting results have been obtained in studies of mononuclear cell infiltration in patients with Crohn disease. Pathologically, Crohn disease is characterized by a pronounced increase in mononuclear cell infiltration through the full thickness of the involved bowel wall.[16,17] Studies of isolated human intestinal mucosal cells from patients with Crohn disease showed a notable increase in the number of B cells, which were predominantly IgG-producing cells, compared with cells from normal persons and patients with other types of inflammatory bowel disease. However, in one study apparently no K or null lymphocytes were found in the intestinal mucosa[17] and gamma globulin production by the isolated mucosal lymphoid cells was notably increased. These results are at variance with earlier results, which suggested that the predominant lymphocyte infiltrating Crohn tissue is a T cell and in fact the plasma cells are predominantly IgM-producing cells.[16] Because of the conflicting results obtained to date, no definite conclusions can be made.

Diagnosis

The diagnosis of Crohn disease is based at present largely on findings from clinical history, physical examination, roentgenograms, and pathologic studies of tissue biopsy specimens. A number of years ago several interesting reports indicated an apparent association between levels of serum lysozyme or muramidase and the presence of clinically active Crohn disease.[18-20] However, a good clinical correlation between the lysozyme level and the disease activity and extent of involvement in patients with Crohn disease has not been borne out[19,20] and, therefore, the serum lysozyme level is not now considered a reliable index for clinical use.

Dr. Ruedi F. Thoeni will now summarize the recent developments in the roentgenographic diagnosis of Crohn disease.

Radiology

DR. THOENI:* When Crohn, in 1932, described the clinical manifestations and pathologic changes associated with idiopathic inflammatory bowel disease, he referred to findings in the terminal ileum. Since then, many articles have appeared in the literature reporting additional manifestations of the disease in the jejunum, duodenum, stomach, colon and, more recently, the esophagus. Determining whether or not a barium enema study is indicated for a patient with inflammatory bowel disease and, if so, preparing for the examination present a problem for many clinicians. Even though toxic megacolon is much less common in patients with Crohn disease than in patients with ulcerative colitis and even though a barium enema has never been proved conclusively to promote development of a toxic megacolon, there still exists the danger of perforating a very friable mucosa.[21-23]

Radiographic examination is indicated in cases in which a diagnosis must be established, the extent of the disease in patients with acute exacerbations must be determined or complications must be identified. In patients with fulminant diarrhea, examinations should be done with the greatest care. At all times, a preliminary roentgenogram of the abdomen must be obtained to rule out toxic megacolon. A barium enema study should not be done in a patient whose transverse colon measures more than 7 cm in diameter. If the patient suffers from fulminant diarrhea with blood loss and other systemic findings but does not show evidence of toxic megacolon, a radiographic study should be carried out only if absolutely necessary.

To prepare a patient, a 24- to 48-hour liquid diet before the study is sufficient. Only mild laxatives, such as bisacodyl in an orally given dose of 10 mg, should be administered in the afternoon before the examination. Some investigators do not administer any cathartic,[23] but if a double-contrast barium enema study is planned, use of laxatives is essential. We administer a water enema half an hour before the radiographic examination by carefully instilling approximately 1,500 to 2,000 ml of water as recommended by Goldberg[23] and Laufer.[24] We introduce the barium slowly through a rubber tip, rather than a hard plastic tip, distending the colon only by gravity and not by volume and thereby avoiding rapid distention. Glucagon, 1 mg given intravenously, may be used if there are areas of suspected strictures.

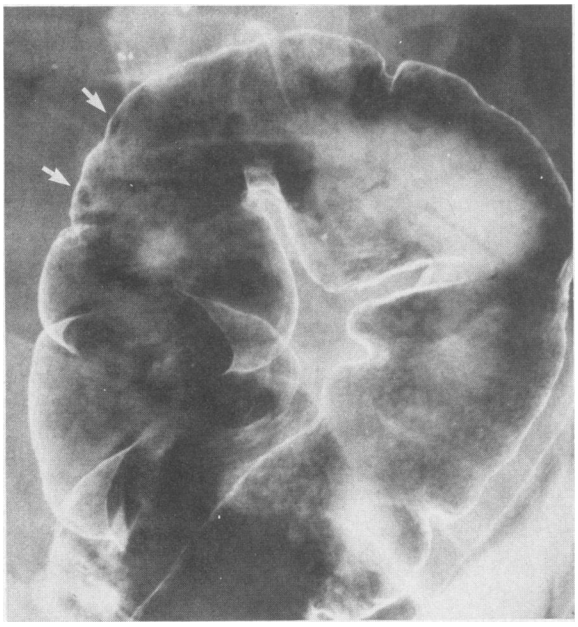

Figure 1.—Double-contrast barium enema study shows aphthoid ulcers **(white arrows)** suggestive of Crohn disease.

In recent years the double-contrast barium enema has been used with increasing frequency to diagnose inflammatory bowel disease, but its usefulness remains controversial.[22,25-27] Use of colonoscopy with a biopsy study allows accurate prediction of the extent of disease. Subtle histologic changes cannot be seen on roentgenograms, but the clinical significance of such microscopic findings has not been established. Double-blind prospective studies comparing findings obtained by double contrast barium enema with those of colonoscopy and biopsy studies are required. Geboes and Vantrappen[28] concluded that colonoscopy is superior to radiography in detection of mucosal changes in patients with Crohn disease; the radiographic results were obtained by secondary double-contrast barium enema examinations. Laufer and co-workers[29] found discrepancies between results of colonoscopy and double-contrast barium enema in only four of 80 patients with clinical evidence of ulcerative colitis or Crohn disease. Examination by double-contrast barium enema involves no more risk to a patient than examination by conventional barium enema.[26]

*Ruedi F. Thoeni, MD, Assistant Professor of Radiology.

Radiologic evidence of "aphthoid" ulcers on a background of normal mucosa (Figure 1), patchy rectal disease, "skip" lesions (Figure 2) and an abnormal terminal ileum (Figure 3) appear to be reliable signs of granulomatous colitis.[24,30] However, these findings are accurate only if the colon is cleaned well and highly dense barium is used. Increased accuracy in diagnosis of colitis leads to appropriate and prompt treatment. In patients with granulomatous colitis, the rectum is often not involved and, consequently, sophisticated, expensive and extensive procedures might be carried out until the correct diagnosis is made. Examination by double-contrast barium enema can prevent this.

It is often impossible to assess the full extent of disease in patients with Crohn disease. Loops of small bowel overlie one another and prevent adequate radiologic visualization. Double-contrast examination of the small bowel via duodenal instillation of air and barium may increase the accuracy of examination of proximal loops of small bowel.[31] Peroral pneumocolon examination of the ileocecal region by oral administration of barium and rectal insufflation of air may increase the accuracy of assessment of this region significantly.[32] Both methods fully distend areas of interest, show mucosal detail and assist in determining whether true stenosis is present or the narrowing is related to spasm representing the so-called "string sign." The correct evaluation of phase and extent of disease permits a clinician to decide on the appropriate therapeutic approach.

An increasing number of reports indicating involvement of the upper gastrointestinal tract in patients with Crohn disease have appeared in recent years.[33-40] A careful search of the literature finds 220 cases of Crohn disease in the upper gastrointestinal tract excluding the small bowel.[33] Of these cases, 57.7 percent involved the duodenum alone, 26.5 percent the duodenum and stomach, and 15.8 percent the stomach alone. In patients with regional enteritis, the overall occurrence of the disease in the esophagus, stomach or duodenum is reported to be between 0.5 percent and 4 percent, and is probably even

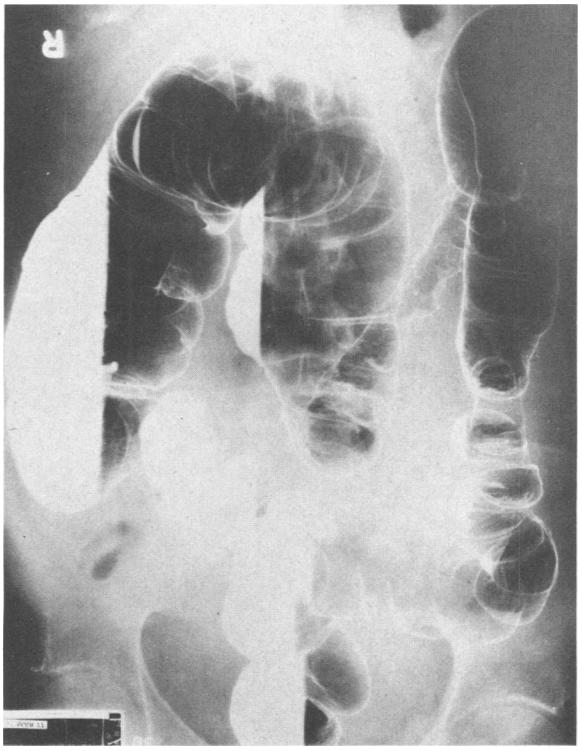

Figure 2.—Double-contrast barium enema study in a patient with Crohn disease. Skip lesions in the distal transverse and descending colon are well outlined.

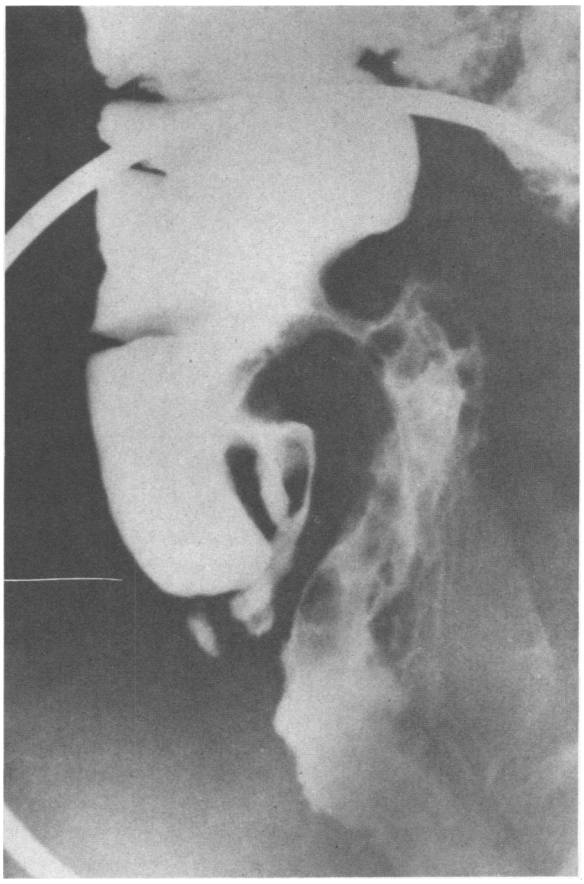

Figure 3.—The cobblestone pattern of the terminal ileum, a classic finding in Crohn disease, is clearly apparent.

Figure 4.—Double-contrast examination of the upper gastrointestinal tract in this patient with Crohn disease of stomach and duodenum shows the pseudo-Billroth I appearance.

higher.[41] However, Marshak[42] did not find Crohn disease of the esophagus in any of his 8,000 cases of regional enteritis and his 4,000 cases of granulomatous colitis. However, we discovered 24 such cases in the literature of which in at least two there were clearly noncaseating granulomas in the resected specimen.[43,44]

Many reports emphasize showing the presence of typical radiographic features in patients with duodenal, gastric and esophageal Crohn disease. In general, the roentgenographic appearance of Crohn disease in these areas is similar to that of regional enteritis in the ileum. The pseudo-Billroth I appearance involving both antrum and duodenum is especially noteworthy (Figure 4).[41] Reflux into biliary and pancreatic ducts may occur.[45,46] When present on radiograms of these areas in patients in whom regional enteritis or granulomatous colitis is known, radiologists should consider the possibility of Crohn disease involving the stomach and proximal bowel.

The differential diagnosis in Crohn disease can be extensive,[38,41,42,47-49] but a correct diagnosis can usually be made by combining all available clinical, roentgenographic and pathologic findings. Double-contrast barium enema, double-contrast examination of the small bowel and peroral pneumocolon examination of the ileocecal region appear to offer advantages that permit early recognition of extent of disease enabling prompt treatment.

Therapy

DR. CELLO: Medical therapy of Crohn disease consists largely of administration of steroids and antibiotics (both nonabsorbable and broad spectrum antibiotics), and alterations in diet, particularly parenteral hyperalimentation when necessary for patients with active disease. Immunosuppressive therapy has been tried in large numbers of patients with Crohn disease but the results are inconclusive.

Steroids and Adrenocorticotropin

Recent studies have suggested that adrenocorticotropin (ACTH) and hydrocortisone are equally efficacious in effecting beneficial clinical responses in patients with Crohn disease. Previous anecdotal reports suggested some superiority of ACTH over steroids, but studies of treatment with 40 units of intravenously given ACTH and 300 mg of intravenously given hydrocortisone resulted in comparable response rates, plasma cortisol levels and onset of clinical improvement.[50] However, the response to ACTH was less in patients who had been receiving steroid therapy previously. Numerous investigators and clinicians believe empirically that steroid therapy is efficacious in treating the acute flare-up of Crohn disease. Despite the indications that the effects of ACTH and steroids are comparable, steroids such as prednisolone and prednisone are preferable to ACTH for the following reasons: ACTH must be administered parenterally to be efficacious; the response to ACTH in terms of plasma cortisol levels depends on the adrenal status; patients who have received steroid therapy previously respond less well to ACTH; the response to ACTH is less, and ACTH cannot be administered as alternate-day therapy. These reasons clearly suggest the superiority of steroids over ACTH.

Sulfasalazine

Sulfasalazine (the newly accepted name for salicylazosulfapyridine) has been used in the treatment of Crohn disease for many years. Approximately 80 percent of the administered drug reaches the colon unchanged. Presumably because of the action of the colonic flora, the drug is converted to 5-amino salicylate, which may have an anti-inflammatory effect, and sulfapyridine, which might have an antibiotic effect.[51] The therapeutic effects of sulfasalazine are controversial. Unlike the findings of the national co-

operative Crohn disease study (see subsequent section), a recent British multicenter trial using sulfasalazine, 3 grams per day, in 41 patients at nine hospitals over five years did not show a decrease in the relapse rate either after surgical operation or with quiescent disease.[52]

Immunosuppressive Therapy

Until recently immunosuppressive therapy for Crohn disease was considered ineffective. Azathioprine has little or no effect on the natural history of the disease.[53,54] It does not induce or sustain a remission and has a high incidence of toxic reactions. Those earlier results are supported by the recent results of the national cooperative Crohn disease study.

Recently, Present and co-workers[55] reported positive results with the immunosuppressive drug 6-mercaptopurine (6-MP) in 83 patients with intractable Crohn disease. The patients were randomly assigned to either a placebo or 6-MP group after having been declared intractable to medical therapy. At the end of one year the "medications" were switched. The results showed significant clinical improvement with 6-MP compared with placebo. In some patients receiving 6-MP it took as long as four to six months to effect a clinical response. However, 6-MP has a high incidence of toxicity manifested by bone marrow suppression, fever and pancreatitis.

A Comparative Study of Steroids, Sulfasalazine and Azathioprine

The recent national cooperative Crohn disease study[56] of various forms of medical therapy was conducted at 14 medical centers in the United States. In 584 patients with Crohn disease a randomized, prospective double-blind controlled trial was carried out. The activity of the disease and the dose of medication used in the study were determined by a weighted aggregate of clinical measurements that are commonly employed in assessing patients with inflammatory bowel disease—the Crohn disease activity index (CDAI). There were two parts to this study: medical treatment of active symptomatic patients was studied in part I and medical prophylaxis in inactive asymptomatic patients was evaluated in part II. The first part consisted of two phases. During part I, phase I, 300 patients who had active symptomatic Crohn disease were assigned for 17 weeks to either a drug or a placebo. Medications were administered as shown in Table 1.

TABLE 1.—*Administration of Medications in Part I, Phase I of Double-blind Study*

Prednisone
CDAI<150 (mild active disease):
0.25 mg per kg of body weight per day or about 20 mg per day for a 70-kg man
CDAI>300 (severe active disease):
0.75 mg per kg of body weight per day or about 60 mg per day
CDAI=150 to 300: 0.50 mg per kg of body weight per day
Sulfasalazine
1 gram per 15 kg of body weight per day or about 5 grams per day for most patients
Azathioprine
2.5 mg per kg of body weight per day or about 150 to 200 mg per day

CDAI=Crohn disease activity index

In part I, phase II, the 95 patients in whom remission was successfully achieved in phase I were followed for an additional one to two years while receiving a lower maintenance dose of the same drug or placebo that had successfully induced the remission. If a flare-up occurred, the dose was raised to phase I level for one month. In part II, 284 patients with inactive asymptomatic Crohn disease were randomly assigned to the aforementioned drugs or placebo to determine the prophylactic value of these agents in preventing flare-ups of the disease.

Results of part I, phase I, showed that prednisone or sulfasalazine, but not azathioprine, caused a significantly better clinical response than placebo in the control of active Crohn disease. Furthermore, only prednisone therapy resulted in significant improvement in the radiographic appearance of the bowel. In patients with Crohn disease of the colon, sulfasalazine was clearly superior to prednisone, azathioprine and placebo in controlling active Crohn disease. In part I, phase II, none of the drugs was superior to placebo in maintaining a remission once it was achieved. In part II no difference was noted between the drug and placebo groups in prevention of relapses. Toxicity with azathioprine was frequent.

Broad Spectrum Antibiotics

At the University of California, San Francisco, broad spectrum antibiotics have been used in patients who did not respond to conventional medical therapy. Although no double-blind controlled study has been carried out, Moss, Carbone and Kressel[57] have reported impressive results in 44

patients treated with ampicillin, tetracycline and clindamycin or erythromycin (or both). Of the 44 patients, there was dramatic clinical improvement in 41, and resolution of radiographic changes occurred in 20 of 35 patients who received various combinations of broad spectrum antibiotics.

Parenteral Hyperalimentation

Parenteral hyperalimentation is commonly used in treating patients with active inflammatory bowel disease,[58-60] but effects have not been evaluated by good, controlled studies. Hyperalimentation causes a decrease in stool frequency. This rests the bowel and may allow closure of enterocutaneous fistulas. In patients who receive hyperalimentation before surgical operation for inflammatory bowel disease, there is improved nutrition with positive nitrogen balance, weight gain and improved fluid and electrolyte balance before and after operation. However, no study has documented a decrease in the necessity of operation in patients with Crohn disease treated with hyperalimentation. Pneumothorax, septicemia, and episodes of hyperglycemia and hypoglycemia are common effects of this method of treatment. Cholestasis with an increase in serum alkaline phosphatase and even acute acalculus cholecystitis have also been reported with hyperalimentation.

Summary

Extensive progress has been made in our understanding of Crohn disease. The most important recent information to date is probably the clinically relevant data obtained in the National Cooperative Crohn's Disease Study. The efficacy of sulfasalazine and prednisone in the treatment of acute disease is now established.

REFERENCES

1. Crohn BB, Ginzburg L, Oppenheimer GD: Regional ileitis—Pathologic and clinical entity. JAMA 19:1323-1329, Oct 1932

2. Farmer GW, Vincent MM, Fuccillo DA, et al: Viral investigations in ulcerative colitis and regional enteritis. Gastroenterology 65:8-18, Jul 1973

3. Gitnik GL, Rosen VJ: Viral investigations in inflammatory bowel disease. Gastroenterology 72:A39/1062, May 1977 (Abstr)

4. Cave DR, Mitchell DN, Brooke BN: Experimental animal studies of the etiology and pathogenesis of Crohn's Disease. Gastroenterology 69:618-624, Sep 1975

5. Mitchell DN, Rees RJW, Goswami KKA: Transmissible agents from human sarcoid and Crohn's disease tissues. Lancet 2:761-765, Oct 1976

6. Taub RN, Sachar D, Janowitz H, et al: Induction of granulomas in mice by inoculation of tissue homogenates from patients with inflammatory bowel disease and sarcoidosis. Ann NY Acad Sci 278:560-564, Sep 1976

7. Mitchell DN, Rees RJW: Further observations on the transmissibility of Crohn's Disease. Ann NY Acad Sci 278:546-559, Sep 1976

8. Parent K, Mitchell PD: Experimental evidence establishing the presence of a wall defective pseudomonas-like bacterial variant in Crohn's disease. Gastroenterology 72:A88/1111, May 1977 (Abstr)

9. Mallas G, Mackintosh P, Asquith P, et al: Histocompatibility antigens in inflammatory bowel disease—Their clinical significance and their association with arthropathy with special reference to HLA-B27 (W27). Gut 17:906-910, Nov 1976

10. MacPherson BR, Albertini RJ, Beeken WL: Immunological studies in patients with Crohn's disease. Gut 17:100-106, Feb 1976

11. Asquith P, Kraft SC, Rothberg RM: Lymphocyte responses to nonspecific mitogens in inflammatory bowel disease. Gastroenterology 65:1-7, Jul 1973

12. Sachar DB, Taub RN, Ramachandar K, et al: T and B lymphocytes and cutaneous anergy in inflammatory bowel disease. Ann NY Acad Sci 278:565-573, Sep 1976

13. Stobo JD, Tomasi TB, Huizenga KA, et al: *In vitro* studies of inflammatory bowel disease—Surface receptors of the mononuclear cell required to lyse allogenic colonic epithelial cells. Gastroenterology 70:171-176, Feb 1976

14. Korsmeyer S, Strickland RG, Wilson ID, et al: Serum lymphocytotoxic and lymphocytophilic antibody activity in inflammatory bowel disease. Gastroenterology 67:578-583, Oct 1974

15. Korsmeyer SJ, Williams RC Jr, Wilson ID, et al: Lymphocytotoxic and RNA antibodies in inflammatory bowel disease: A comparative study in patients and their families. Ann NY Acad Sci 278:574-585, Sep 1976

16. Meuwissen SGM, Feltkamp-Vroom TM, Brutol de la Riviere A, et al: Analysis of the lymphoplasmacytic infiltrate in Crohn's disease with special reference to identification of lymphocyte-subpopulations. Gut 17:770-780, Oct 1976

17. Bookman MA, Helms RA, Bull DM: Isolated human intestinal mucosal lymphoid cells: Alterations in inflammatory bowel disease. Gastroenterology 72:A132/1155, May 1977

18. Falchuk KR, Perrotto JL, Isselbacher KJ: Serum lysozyme in Crohn's disease and ulcerative colitis. N Engl J Med 292:395-397, Feb 20, 1975

19. Hylander E, Hansen NE, Karle H, et al: Serum lysozyme in Crohn's disease and ulcerative colitis. Scand J Gastroenterol 11:213-217, Feb 1976

20. Nugent FW, Mallari R, George H, et al: Serum lysozyme in inflammatory bowel disease. Gastroenterology 70:1014-1016, Jun 1976

21. Javett SL, Brooke ON: Acute dilatation of the colon in Crohn's disease. Lancet 2:126-128, Jul 1970

22. Marshak RH, Lindner AE: Roentgen features of granulomatous colitis and ileocolitis, *In* Bercovitz ZT, Kirsner JB, Lindner AE, et al (Eds): Ulcerative and Granulomatous Colitis, Springfield, Ill., Charles C Thomas, 1973, pp 105-175

23. Goldberg HI: The barium enema and toxic megacolon: Cause-effect relationship? (Letter) Gastroenterology 68:617-618, Mar 1975

24. Laufer I: Air contrast studies of the colon in inflammatory bowel disease. Crit Rev Diag Imag 9:421-447, Aug 1977

25. Laufer I: In support of double contrast enema (Letter). Gastrointest Radiol 1:393, May 1977

26. Beranbaum SL: Roentgenologic diagnosis of idiopathic, nonspecific ulcerative colitis, with special reference to early manifestations. Dis Colon Rectum 7:135-146, Mar-Apr 1964

27. Fennessy JJ, Sparberg M, Kirsner JB: Early roentgen manifestations of mild ulcerative colitis and proctitis. Radiology 87:848-858, Nov 1966

28. Geboes K, Vantrappen G: The value of colonoscopy in the diagnosis of Crohn's disease. Gastrointest Endosc 22:18-23, Aug 1975

29. Laufer I, Mullens JE, Hamilton J: Correlations of endoscopy and double-contrast radiography in the early stages of ulcerative and granulomatous colitis. Radiology 118:1-5, Jan 1976

30. Laufer I: The radiologic demonstration of early changes in ulcerative colitis by double contrast technique. J Can Assoc Radiol 26:116-121, Jun 1975

31. Ekberg O: Crohn's disease of the small bowel examined by double contrast technique: A comparison with oral technique. Gastrointest Radiol 1:355-359, May 1977

32. Kellett MJ, Zboralski FF, Margulis AR: Peroral pneumocolon examination of the ileocecal region. Gastrointest Radiol 1:361-365, May 1977

33. Bagby RJ, Rogers JV Jr, Hobbs C: Crohn's disease of the esophagus, stomach and duodenum: A review with emphasis on the radiographic findings. South Med J 65:515-523, May 1972

34. Danzi JT, Farmer RG, Sullivan BH Jr, et al: Endoscopic features of gastroduodenal Crohn's disease. Gastroenterology 70:9-13, Jan 1976

35. Farman J, Faegenburg D, Dallemand S, et al: Crohn's disease of the stomach: The "ram's horn" sign. Am J Roentgenol 123:242-251, Feb 1975

36. Heffernon EW, Kepkay PH: Segmental esophagitis, gastritis and enteritis. Gastroenterology 26:83-88, Jan 1954

37. Legge DA, Carlson HC, Judd ES: Roentgenologic features of regional enteritis of the upper gastrointestinal tract. Am J Roentgenol 110:355-360, Oct 1970

38. Madden JL, Ravid JM, Haddad JR: Regional esophagitis: A specific entity simulating Crohn's disease. Ann Surg 170:351-368, Sep 1969

39. Rösch W: Crohn's disease of the upper gastrointestinal tract. Acta Hepato Gastroenterol (Stuttg) 20:254-257, May-Jun 1973

40. Rosendorff C, Grieve NWT: Ulcerative oesophagitis in association with ulcerative colitis. Gut 8:344-347, Aug 1967

41. Thompson WM, Cockrill H Jr, Rice RP: Regional enteritis of the duodenum. Am J Roentgenol 123:252-261, Feb 1975

42. Marshak RH: Granulomatous disease of the intestinal tract (Crohn's disease)—Annual oration in honor of Benjamin H. Orndorff, M.D. (1881-1971). Radiology 114:3-22, Jan 1975

43. Cynn W-S, Chon HK, Gureghian PA, et al: Crohn's disease of the esophagus. Am J Roentgenol 125:359-364, Oct 1975

44. LiVolsi VA, Jaretzki A III: Granulomatous esophagitis—A case of Crohn's disease limited to the esophagus. Gastroenterology 64:313-319, Feb 1973

45. Legge DA, Hoffman HN, Carlson HC: Pancreatitis as a complication of regional enteritis of the duodenum. Gastroenterology 61:834-837, Dec 1971

46. Nelson SW: Some interesting and unusual manifestations of Crohn's disease ("regional enteritis") of the stomach, duodenum, and small intestine. Am J Roentgenol 107:86-101, Sep 1969

47. Marshak RH: Question of double contrast enema (Letter). Gastrointest Radiol 1:393, May 1977

48. Marshak RH, Lindner AE: Regional enteritis, *In* Margulis AR, Burhenne HJ (Eds): Alimentary Tract Roentgenology, 2nd Ed. St. Louis, CV Mosby Co., 1973, pp 819-841

49. Vantrappen G, Agg HO, Ponette E, et al: Yersinia enteritis and enterocolitis: Gastroenterological aspects. Gastroenterology 72:220-227, Feb 1977

50. Kaplan HP, Portnoy B, Binder HJ, et al: A controlled evaluation of intravenous adrenocorticotropic hormone and hydrocortisone in the treatment of acute colitis. Gastroenterology 69:91-95, Jul 1975

51. Das KM, Sternlieb I: Salicylazosulfapyridine in inflammatory bowel disease. Am J Dig Dis 20:971-976, Oct 1975

52. Sulfasalazine in asymptomatic Crohn's disease—A multicentre trial. Gut 18:69-72, Jan 1977

53. Klein M, Binder HJ, Mitchell M, et al: Treatment of Crohn's disease with azathioprine: A controlled evaluation. Gastroenterology 66:916-922, May 1974

54. Brooke BN, Cave DR, King DW: Place of azathioprine for Crohn's disease. Lancet 2:1041-1042, May 1976

55. Present DH, Wisch N, Glass JL, et al: The efficacy of immuno-suppressive therapy in Crohn's disease—A randomized long term double blind study. Gastroenterology 72:A91/1114, May 1977 (Abstr)

56. National Cooperative Crohn's Disease Study (NCCDS): Results of drug treatment—A cooperative study. Gastroenterology 72:A110/1133, May 1977 (Abstr)

57. Moss AA, Carbone JV, Kressel HY: Successful treatment of Crohn's disease with broad-spectrum antibiotics: Initial and long-term results. Gastroenterology 72:A83/1106, May 1977 (Abstr)

58. Anderson DL, Boyce HW Jr: Use of parenteral nutrition in treatment of advanced regional enteritis. Am J Dig Dis 18:633-640, Aug 1973

59. Fazio VW, Kodner I, Jagelman DJ, et al: Parenteral nutrition as primary or adjunctive treatment. Dis Colon Rectum 19:574-578, Oct 1976

60. Vogel CM, Corwin TR, Baue AE: Intravenous hyperalimentation in the treatment of inflammatory diseases of the bowel. Arch Surg 108:460-467, Apr 1974

Clues in Cultures of Blood Specimens

THERE ARE CLUES that one can use as to what type of blood specimen culture to take in a patient. The age of a patient may give you a clue as to what organisms to suspect. Certainly a newborn infant has a different kind of flora that causes infection and disease than does a child or an older patient. In newborns there are two organisms that are responsible for almost all of the serious infections—the enteric Gram-negatives, with Escherichia coli being the most common, and then the streptococci—so that you could predict pretty well what kind of organism you might find in a newborn suspected of having sepsis. It becomes a little more difficult as the child grows older. Children are likely to be infected with a wider variety of organisms and certainly adults are affected with an even wider variety. But one also has additional clues. Is the patient in the hospital or is he coming in from the outside? The patient who is in the hospital is exposed to organisms which you know are going to be common organisms associated with infection in the intensive care unit—the pseudomonades, the enterobacteria—those organisms which because of the hospital environment have the opportunity to get into the patient. And then, of course, the history of the patient is important: Are you dealing with a patient who has a chronic underlying disease and therefore is susceptible to a group of organisms that may require a different type of cultural technique for identification? Is there a skin rash that could give you a clue as to what type of organisms you might be dealing with in a systemic infection? In any case, there are two or three additional things that might be used as clues to a bacterial infection.

—ALLEN W. MATHIES, JR, MD, *Los Angeles*

Extracted from *Audio-Digest Internal Medicine*, Vol. 24, No. 19, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.